

Obesity and cancer risk among white and black United States veterans

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Abstract

Background: Obesity has been linked to excess risk for many cancers, but the evidence remains tenuous for some types. Although the prevalence of obesity varies by race, few studies of obesity-related cancer risk have included non-white subjects.

Methods: In a large cohort of male US veterans (3,668,486 whites; 832,214 blacks) hospitalized with a diagnosis of obesity between 1969 and 1996, we examined risk for all major cancer sites and subsites. Person-years accrued from the date of first obesity diagnosis until the occurrence of a first cancer, death, or the end of the observation period (September 30, 1996). We calculated age- and calendar-year adjusted relative risks (RR) and 95% confidence intervals (CI) for cancer among white and black veterans, comparing obese men to men hospitalized for other reasons, with obesity status as time-dependent. For selected cancers, we performed additional analyses stratified by specific medical conditions related to both obesity and risk of those cancers. To determine whether obesity-related cancer risks differed significantly between white and black men, we evaluated heterogeneity of risk for each cancer site.

Results: Among white veterans, risk was significantly elevated for several cancers, including cancers of the lower esophagus, gastric cardia, small intestine, colon, rectum, gallbladder and ampulla of vater, male breast, prostate, bladder, thyroid, and connective tissue, and for malignant melanoma, multiple myeloma, chronic lymphocytic leukemia (CLL), and acute myeloid leukemia (AML). Excess risks initially observed for cancers of the liver and pancreas persisted among men without a history of diabetes or alcoholism. Among black veterans, risks were significantly elevated for cancers of the colon, extrahepatic bile ducts, prostate, thyroid, and for malignant melanoma, multiple myeloma, CLL and AML.

Conclusions: Obese men are at increased risk for several major cancers as well as a number of uncommon malignancies, a pattern generally similar for white and black men. Due to the increasing prevalence of obesity and overweight worldwide, it is important to clarify the impact of excess body weight on cancer and to elucidate the mechanisms involved.

Introduction

The prevalence of obesity in the United States has steadily increased over the past 20 years among adults and children of all racial and ethnic groups, and has become a major public health concern [1]. It is well-known that obesity increases the risk of cardiovascular

disease, diabetes mellitus, and overall mortality [2], but the relationship between obesity and various cancers is less well understood. Although a number of studies have linked obesity with increased risks for some major cancers, especially of the colon, breast, endometrium and kidney [3, 4], few studies have examined the obesity-related risk of less common cancers [5–8].

The prevalence of obesity varies by age, sex and race. Although the overall prevalence is similar among white and black men, it is higher among black men between the ages of 20 and 50 years [9]. Prevalence of obesity is higher among black women of all ages compared to

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white women [10]. In addition, among children and adolescents, the prevalence of obesity is slightly higher among black than white males and females [1]. Cancer incidence also varies by race, being higher among black men than white men for many types of cancer [11]. Despite racial differences in the prevalence of obesity and cancer incidence, studies of obesity and cancer risk have typically been conducted among European or American white populations [5–8]. The purpose of this study is to assess site-specific cancer risks in a large cohort of white and black US veterans who had a hospital discharge diagnosis of obesity, and who were followed for up to 27 years.

Materials and methods

The study cohort was selected from computerized discharge records for inpatient visits at Veterans Affairs (VA) hospitals across the United States between July 1, 1969 and September 30, 1996. Diagnoses were coded according to the 8th and 9th revision of the International Classification of Diseases (ICD8-A, ICD9-CM). Subjects were defined as obese if, during any visit, they received a discharge diagnosis of obesity (ICD8 = 277, ICD9 = 278.0).

All veterans with at least one hospital visit ($n = 5,790,493$) were initially selected for inclusion. Since the number of female veterans in the database was too small for detailed analyses of cancer incidence, they were excluded from the study. In addition, male veterans whose race was other than white or black were also excluded due to small numbers in each racial category. After additional exclusions of individuals whose race could not be determined ($n = 62,622$; $<2\%$), individuals with discrepant records ($n = 887$; $<1\%$), and individuals whose age at cohort entry was less than 18 or greater than 100 ($n = 3003$; $<1\%$), a total of 4,500,700 white and black male veterans with at least one year of follow-up met the cohort definition, and were considered eligible for study.

Follow-up began with the date of the first hospital discharge and continued until the diagnosis of a first cancer, death, or the end of the observation period, whichever came first. Obesity status was treated as a time-dependent variable, with person-years allocated to the non-obese category until such time an obesity diagnosis was made, after which person-years were allocated to the obese category. Cancers diagnosed during the first hospital visit and during the first year of follow-up were excluded as prevalent cancers, while cancers diagnosed during years 2–27 were considered incident cases and included in this analysis. In addition,

in order to exclude cancers which occurred close in time to obesity, we excluded those cancers diagnosed within one year of obesity diagnosis.

Dates of death were obtained from VA hospital records, and by linkage to Social Security Administration mortality files. Using Poisson methods for cohort data [12], race-specific relative risks (RR) and 95% confidence intervals (95% CI) were calculated, adjusting for age and calendar-year, comparing the cancer risks among obese men to risks among men who were not identified as obese. In order to evaluate the effects of alcoholism, diabetes and hypertension, conditions that may either confound the obesity-cancer association or perhaps be part of the causal pathway, we analyzed the risks of selected cancers while stratifying by the presence or absence of these conditions. Variables for all diagnoses were based upon dates of hospital discharge for these conditions; therefore, all variables were time-dependent with the exception of race. To determine whether obesity-related cancer risks differed significantly between white and black men, we evaluated homogeneity of risk for each cancer site by including an interaction term for obesity and race. The present study was approved by the Institutional Review Board of the National Cancer Institute.

Results

A total of 4,500,700 veterans (3,668,486 white; 832,214 black) were included in the analysis (Table 1). Subjects were followed for up to 27 years, with an average of 12 years per subject. On average, black men tended to be younger than white men at study entry, but average age at first cancer diagnosis was similar for both groups. Black men were diagnosed with obesity at a slightly younger age than white men. Only 6% of obesity diagnoses were listed as the primary reason for hospital admission; the large majority (94%) were secondary to associated conditions, most commonly alcoholism, diabetes, and hypertension. Obese men tended to visit the hospital twice as much as non-obese men.

Among white veterans, obese men had a 7% significant excess risk for all cancers combined (Table 2). Risks were significantly elevated for several cancers, including the colon (RR = 1.5), pancreas (RR = 1.2), prostate (RR = 1.2), and kidney (RR = 1.6). For esophageal cancers, a significant excess risk was confined to tumors arising from the lower esophagus (RR = 1.4), whereas for stomach cancer, a significant excess risk was limited to tumors of the cardia (RR = 1.4). The majority of kidney cancers were renal cell carcinomas (RRC,

Table 1. Characteristics of the study cohort (US Veterans Affairs): white and black male veterans with at least one hospital admission between July 1, 1969 and September 30, 1996, who were followed up to 27 years

Characteristics	White veterans		Black veterans	
	Non-obese	Obese	Non-obese	Obese
No. of subjects	3,456,979	211,507	797,472	34,742
Years of follow-up (mean)	11.6	12.7	11.8	13.4
Person years at risk	40,665,254	2,084,083	9,527,566	358,756
Mean age at study entry	52.2	51.8	47.6	48.4
Mean age at first cancer diagnosis	66.2	66.1	64.7	65.9
Mean age at obesity		54.6		51.5
Median number of hospital visits	3	6	3	6
% ever diagnosed with selected co-diagnoses				
Alcoholism	23.9	26.1	30.4	26.3
Diabetes	11.4	37.4	13.5	44.9
Hypertension	20.7	52.2	30.4	68.7

RR = 1.7). For colon cancer, excess risks were observed across all subsites.

In addition, excess risks were observed for cancers of the small intestine (RR = 1.6), particularly the duodenum (RR = 2.1), and of the rectum (RR = 1.2), liver (RR = 1.4), gallbladder (RR = 1.7) and ampulla of vater (RR = 1.6), male breast (RR = 2.6), bladder (RR = 1.1), thyroid (RR = 1.4), adrenal gland (RR = 2.2), and connective tissue (RR = 1.3), and for malignant melanoma (RR = 1.3), multiple myeloma (RR = 1.2), and leukemia (RR = 1.4). Excess leukemia risk was confined to chronic lymphocytic leukemia (CLL) (RR = 1.3) and acute myeloid leukemia (AML) (RR = 1.6). Risks were significantly reduced for cancers of the buccal cavity (RR = 0.7), larynx (RR = 0.8), and lung (RR = 0.9).

In contrast to obese white veterans, overall cancer risk was slightly reduced for obese black veterans (RR = 0.8) (Table 2). However, the general pattern of cancer incidence was similar to obese white men, with significant excess risks noted for cancers of the colon (RR = 1.4), particularly the cecum/ascending (RR = 1.6) and sigmoid subsites (RR = 1.6), and of the extrahepatic bile ducts (RR = 2.2), prostate (RR = 1.1), kidney (RR = 1.3), and thyroid (RR = 1.9), and for malignant melanoma (RR = 2.4), multiple myeloma (RR = 1.3), CLL (RR = 1.7) and AML (RR = 2.6). As among white men, the majority of kidney cancers were RRC (RR = 1.4). Risks were significantly reduced for cancers of the buccal cavity (RR = 0.3), and the upper (RR = 0.3), middle (RR = 0.5) and lower esophagus (RR = 0.2), as well as the larynx (RR = 0.5) and lung (RR = 0.6).

We evaluated the effect of latency based on intervals of 1–4 and 5 or more years of follow-up after obesity diagnosis. For all cancers, risk patterns remained consistent across both periods of follow-up (data not

shown). In order to determine whether risk estimates were affected by differences in VA hospital utilization and follow-up for veterans who were also eligible to receive Medicare benefits, we restricted the analyses to person-years that accumulated prior to 65 years of age. The only notable change was for lung cancer risk, which was further reduced among both white and black men.

Table 3 shows results stratified by alcoholism, diabetes and hypertension. Among white men, the excess risk observed for cancer of the lower esophagus was seen among non-alcoholics while no association was observed among alcoholics. Obesity-related risk for liver cancer was seen among both alcoholics and non-alcoholics, although the risk was higher in the alcoholic group. When stratifying by history of diabetes, obesity-related risk for cancers of the liver and pancreas remained significantly elevated among non-diabetics while no association was seen among diabetics. Risk of renal cell cancer was significantly elevated among white veterans with and without hypertension.

Among black men there was a deficit of esophageal cancer among both alcoholics and non-alcoholics. The overall deficit of liver cancer persisted among non-alcoholics, while no obesity-related risk was observed in the alcoholic group. Liver cancer was inversely associated with obesity among both diabetics and non-diabetics, while no association was observed for pancreas cancer. Risk of renal cell cancer was slightly elevated among black men with hypertension but not among those without hypertension.

To examine differences in obesity-related cancer risk between white and black men, we tested for heterogeneity of the RR for each cancer site. For most cancer sites, there were no significant differences in risk between whites and blacks, with a few exceptions (Table 2). Obesity-related risk for all cancers combined was

Table 2. RR and 95% CI for major cancer types among obese (ICD8 = 277, ICD9 = 278.0) veterans compared to non-obese veterans, followed for 1–27 years (1969–1996)^a

Cancer (ICD)	White men			Black men			RR	(95% CI)	p-Value ^b
	Cases among		RR	Cases among		RR			
	Obese	Non-obese		Obese	Non-obese				
All cancers (140–208)	17,882	279,684	1.07	(1.05–1.09)	2853	69,854	0.85	(0.81–0.88)	<0.001
Buccal (140–149)	957	22,841	0.69	(0.64–0.73)	80	5281	0.31	(0.25–0.39)	<0.001
Salivary (142)	60	836	1.24	(0.95–1.62)	10	158	1.38	(0.73–2.62)	NS
Nasopharynx (147)	32	578	0.91	(0.64–1.31)	6	165	0.76	(0.34–1.73)	NS
Esophagus (150)	318	6000	0.87	(0.77–0.97)	67	3936	0.34	(0.27–0.44)	<0.001
Upper (150.0, 150.3)	16	371	0.69	(0.42–1.14)	3	191	0.31	(0.10–0.97)	NS
Middle (150.1, 150.4)	23	508	0.72	(0.48–1.10)	12	466	0.51	(0.29–0.91)	NS
Lower (150.2, 150.5)	103	1175	1.40	(1.15–1.72)	4	460	0.18	(0.06–0.47)	<0.001
Stomach (151)	309	4989	1.07	(0.95–1.20)	99	2089	0.98	(0.79–1.20)	NS
Cardia (151.0)	72	841	1.38	(1.09–1.77)	5	131	0.78	(0.32–1.91)	NS
Other (151.x)	237	4148	1.00	(0.88–1.14)	94	1958	0.99	(0.80–1.22)	NS
Small intestine (152)	49	520	1.58	(1.18–2.12)	9	180	1.07	(0.54–2.08)	NS
Duodenum (152.0)	25	193	2.10	(1.38–3.22)	4	84	1.01	(0.37–2.77)	NS
Colon (153)	1420	16,702	1.47	(1.39–1.55)	262	3830	1.45	(1.28–1.64)	NS
Cecum/ascending (153.4, 153.6)	353	3878	1.60	(1.44–1.79)	67	885	1.60	(1.25–2.06)	NS
Transverse (153.0, 153.1, 153.7)	204	1992	1.74	(1.51–2.02)	31	490	1.35	(0.94–1.94)	NS
Descending (153.2)	77	786	1.70	(1.35–2.15)	12	205	1.22	(0.68–2.19)	NS
Sigmoid (153.3)	435	5067	1.46	(1.33–1.62)	71	947	1.56	(1.22–1.99)	NS
Rectum (154)	719	9849	1.23	(1.14–1.33)	93	1773	1.11	(0.90–1.37)	NS
Liver and intrahepatic bile ducts (155)	322	3612	1.44	(1.28–1.61)	38	1168	0.68	(0.49–0.94)	<0.001
Gallbladder (156.0)	26	265	1.70	(1.13–2.57)	2	45	0.93	(0.23–3.86)	NS
Extrahepatic bile ducts (156.1)	27	348	1.36	(0.92–2.02)	7	69	2.24	(1.03–4.89)	NS
Ampulla of Vater (156.2)	24	239	1.63	(1.06–2.51)	4	41	2.07	(0.74–5.78)	NS
Pancreas (157)	391	5483	1.20	(1.07–1.33)	83	1638	1.07	(0.86–1.34)	NS
Larynx (161)	515	10,555	0.77	(0.71–0.85)	67	2612	0.51	(0.40–0.65)	0.001
Lung, trachea and bronchus (162)	4398	78,205	0.91	(0.88–0.94)	568	18,884	0.60	(0.55–0.65)	<0.001
Connective tissue (171)	185	2561	1.27	(1.09–1.48)	20	384	1.14	(0.72–1.80)	NS
Malignant melanoma (172) ^c	273	3728	1.29	(1.14–1.46)	10	86	2.39	(1.20–4.75)	NS
Breast (174, 175)	50	324	2.59	(1.92–3.49)	6	79	1.31	(0.53–3.24)	NS
Prostate (185)	3206	45,901	1.19	(1.15–1.24)	815	15,272	1.12	(1.04–1.20)	NS
Bladder (188)	1087	16,260	1.13	(1.06–1.20)	72	1796	0.85	(0.67–1.08)	NS
Kidney (189)	598	6115	1.61	(1.48–1.75)	87	1351	1.32	(1.06–1.65)	NS
Renal cell (189.0)	508	4784	1.74	(1.58–1.90)	77	1151	1.38	(1.09–1.74)	NS
Brain (191)	207	3639	0.98	(0.85–1.13)	23	487	1.04	(0.68–1.58)	NS
Thyroid (193)	64	811	1.40	(1.09–1.81)	13	156	1.92	(1.09–3.40)	NS
Adrenal (194.0)	29	231	2.21	(1.50–3.26)	3	55	1.30	(0.40–4.17)	NS
NHL (200, 202)	449	7511	1.03	(0.94–1.14)	71	1425	1.17	(0.92–1.49)	NS
Hodgkin's disease (201)	70	1239	1.11	(0.87–1.41)	14	248	1.39	(0.79–2.43)	NS
Multiple myeloma (203)	204	2817	1.22	(1.05–1.40)	89	1509	1.26	(1.02–1.56)	NS

Table 2. (Continued)

Cancer (ICD)	White men			Black men			p-Value ^b
	Cases among		RR	Cases among		RR	
	Obese	Non-obese		Obese	Non-obese		
All leukemia (204-208) ^d	630	7687	1.42	109	1364	1.77	0.05
ALL (204.0)	18	245	1.33	1	37	0.69	NS
CLL (204.1)	222	2918	1.30	39	487	1.72	NS
AML (205.0)	138	1469	1.59	30	257	2.64	<0.05
CML (205.1)	77	1186	1.15	14	239	1.32	NS

^a Controlling for age and calendar year.

^b p-Value for test of heterogeneity of risk between white and black veterans.

^c ICD – Excluding non-melanoma skin cancer and metastatic cancers.

^d ALL – acute lymphocytic leukemia; CLL – chronic lymphocytic leukemia; AML – acute myeloid leukemia; CML – chronic myeloid leukemia.

slightly elevated among white men, but slightly lowered among black men. There was an inverse association for cancers of the buccal cavity, larynx, and lung among obese men of both races, and this association was more pronounced among black men. In addition, the risk of esophageal cancer was generally reduced in both races, except for the significantly elevated risk of lower esophageal cancer among white men. Obesity-related risk for liver cancer was significantly elevated among white men but appeared to be decreased among black men. Obesity-related risks for leukemia tended to be greater among black men than white men for all cell types, with the only significant difference observed for AML.

Discussion

Our cohort study of military veterans in the United States, one of the largest studies to investigate cancer incidence among white and black men, revealed excess risks associated with obesity for several major cancers. For most tumors, the obesity-related patterns of risk were similar among black and white men.

The excess risk of lower esophageal cancer among obese white men is consistent with results from previous studies [8, 13–16]. Although histologic data were not generally available in this study, most cancers among whites arising from the lower esophagus are adenocarcinomas [15]. The obesity-related risk of lower esophageal cancer in our study was seen only among those without a co-diagnosis of alcoholism. Obesity has been associated with gastroesophageal reflux disease which predisposes to Barrett’s esophagus, a metaplastic precursor to esophageal adenocarcinoma, while alcoholism is a major risk factor for squamous cell carcinoma of the esophagus [15]. The lack of association between obesity and lower esophageal cancers among alcoholics may be due to the fact that most tumors among alcoholics are of the squamous cell type. The inverse association observed for lower esophageal cancer among black veterans is likely due to the small number of cases with subsite classification, and a much higher proportion of esophageal squamous cell carcinoma than adenocarcinoma among black men [17].

The excess risk of stomach cancer observed for obese white men was confined to cancers of the gastric cardia, while no association was seen for non-cardia tumors, consistent with previous studies indicating similar risk factors for esophageal and gastric cardia adenocarcinomas [13–15]. Although numbers were relatively small, a significant excess of small bowel cancer, especially of the duodenum, was observed among white veterans. This

Table 3. RR and 95% CI for selected cancers for obese veterans compared to non-obese veterans, stratified by various medical conditions^a

Cancer site	White men						Black men					
	No alcoholism			Alcoholism ^b			No alcoholism			Alcoholism ^b		
	Obese cases	RR	(95% CI)	Obese cases	RR	(95% CI)	Obese cases	RR	(95% CI)	Obese cases	RR	(95% CI)
Esophagus	205	0.96	(0.83–1.10)	113	0.72	(0.59–0.86)	38	0.36	(0.26–0.49)	29	0.41	(0.28–0.60)
Upper	7	0.65	(0.30–1.38)	9	0.68	(0.35–1.34)	2	0.40	(0.10–1.61)	1	0.26	(0.04–1.88)
Middle	14	0.92	(0.54–1.58)	9	0.52	(0.27–1.02)	6	0.58	(0.27–1.22)	6	0.54	(0.22–1.32)
Lower	75	1.62	(1.28–2.04)	28	0.99	(0.67–1.47)	2	0.16	(0.04–0.66)	2	0.23	(0.06–0.93)
Liver	148	1.26	(1.07–1.49)	174	1.58	(1.34–1.85)	22	0.61	(0.40–0.93)	16	0.96	(0.58–1.58)
	No diabetes			Diabetes ^b			No diabetes			Diabetes ^b		
Liver	153	1.25	(1.07–1.47)	169	0.96	(0.81–1.15)	16	0.55	(0.34–0.90)	22	0.59	(0.38–0.92)
Pancreas	219	1.17	(1.03–1.34)	172	0.87	(0.73–1.03)	39	0.98	(0.72–1.34)	44	0.88	(0.64–1.20)
	No hypertension			Hypertension ^b			No hypertension			Hypertension ^b		
Renal cell	219	1.66	(1.46–1.90)	289	1.24	(1.08–1.41)	16	0.96	(0.58–1.57)	61	1.11	(0.85–1.45)

^a Controlling for age and calendar year.

^b Person-years accrued prior to diagnosis of alcoholism, diabetes mellitus, or hypertension were allocated to the non-diseased group. Once a veteran was diagnosed with one of these conditions, his person-years were allocated to the diseased group.

finding resembles a recent cohort study of obese individuals in Sweden that reported a significantly elevated risk for cancers of the small intestine, particularly of the duodenum [7].

A number of studies have reported an increased risk of colon cancer among men with an elevated BMI [8, 18], although the results for colon subsites have been mixed [19–22]. Our findings suggest that obese men are prone to colon cancer across all subsites. Although most studies have not reported a relationship between obesity and rectal cancer [7, 8, 19, 23, 24], the elevated risk we observed among obese white veterans is consistent with findings from the Swedish cohort study [7].

Obesity has been related to cancers of the pancreas and liver in some studies [7, 8, 25–27], although it has been suspected that conditions such as alcoholism and diabetes may have confounded these associations [8]. Results for white men in our study suggest that in the absence of alcoholism and diabetes, obesity may confer some risk for these cancers. The finding for pancreas cancer is consistent with the significant trend of increasing risk associated with increasing BMI observed among non-diabetics in a recent case-control study [28].

Reasons for the apparent deficit of liver cancer among black men are unclear. In the United States, the incidence of liver cancer is higher among African-Americans compared to Caucasians, and higher among men than women [29]. The excess risk of biliary tract cancer among obese veterans, especially of the gallbladder and ampulla of Vater among white men and extrahepatic bile duct cancer among black men, is

consistent with previous studies relating these tumors to obesity [30].

The incidence of connective tissue cancers was elevated among obese white men in our study, also consistent with findings from the Swedish cohort study [7]. In contrast to the Swedish and Danish cohorts [7, 8], we observed significant excess risks of melanoma among obese white and black men. These findings are in agreement with results from two other studies of melanoma [31, 32], and suggest that obesity should be further evaluated as a risk factor for this cancer. Our results linking obesity with male breast cancer are consistent with a case-control study suggesting a significant dose-response relationship with increasing BMI [33].

The excess risk of prostate cancer among obese veterans is in agreement with findings from some studies [34, 35], but not with others [36, 37]. Our study also pointed to an excess risk for bladder cancer among obese white men, but there is little supporting evidence for this association in the literature. However, a positive association between body weight and bladder cancer was reported in an extended follow-up of college graduates [6], and an excess risk was observed for obese women in the Swedish cohort study [7].

Our study of obese veterans also revealed an excess risk of RCC, consistent with a number of previous studies that have clearly linked risk of kidney cancer to elevations in body mass index [3, 6–8, 38–40]. To our knowledge, prior studies have not examined the association between obesity and RCC in the black population,

which has higher rates of RCC and hypertension (an important risk factor) compared to the white population [39, 41]. Although obesity-related risk of RCC was evident among white veterans with and without hypertension, the risk among black veterans was confined to those with hypertension. It is unclear why this pattern differed among white and black men.

Our results suggested an increased risk of thyroid cancer among obese men, consistent with an association seen in some previous studies [42, 43]. In addition, among both white and black men in our study, obesity was associated with an increased risk of multiple myeloma, consistent with some previous studies [44, 45].

The excess risk of leukemia in our study involved CLL and AML, and affected both white and black men. While the Danish cohort study noted a significant excess of leukemia (RR = 1.3), there was no analysis by subtype [8]. Our findings are interesting in view of the relation between high birth weight and childhood leukemia [46, 47], a report linking high BMI to acute promyelocytic leukemia [48], and a recent prospective study from Iowa suggesting a relation between elevated BMI and CLL [49].

The major strengths of our study include its prospective design, large size, length of follow-up, and ability to assess site-specific cancer risks among white and black men. Although it is the largest study to date that has been able to examine obesity-related cancer incidence in white and black men, our sample size was too small for a precise analysis of the associations between obesity and uncommon cancers, particularly among black men. Since BMI or other anthropometric measurements were unavailable, the use of hospital diagnoses of obesity as our measure of exposure suggests that the study subjects were most likely severely obese and that our comparison group contains veterans with marginal obesity, which would tend to dilute RR estimates. On the other hand, obese men tended to be hospitalized twice as often as non-obese men due to co-morbid medical conditions, which may have led to increased cancer detection and overestimation of obesity-related risk.

Another limitation of our study is the lack of systematic follow-up which may have resulted in incomplete cancer ascertainment. Risk estimates for certain cancers may have been affected by differences in hospital utilization and follow-up since veterans who were diagnosed with cancer outside of the VA health system would be excluded. However, the VA population tends to be poorer than the general population and to lack alternative forms of health insurance [50] and therefore less likely to leave the VA system [51]. Although obesity has been inversely associated with SES this relationship is less apparent among men than women [52]. It is

therefore unclear whether follow-up of obese and non-obese veterans in our study differed. Our results did not change after restricting the analysis to veterans less than 65 years of age, suggesting little effect resulting from loss to follow-up due to Medicare eligibility. Since our records are based solely in inpatient diagnoses, it is possible that more fatal cancers (*e.g.* lung, liver) are heavily represented while cancers such as melanoma, which are commonly detected in outpatient settings, may have been inadequately captured.

Data on potential confounding factors were not available, the most significant of which is cigarette smoking. Given the established inverse association between smoking and body weight [53], it is possible that differential smoking prevalence between obese and non-obese veterans would underestimate the risks associated with smoking-related cancers. Any confounding due to smoking may have been more pronounced for black veterans if smoking prevalence were higher among blacks than whites [54]. Similar to smoking, differential prevalence of other unmeasured confounders could have resulted in an over- or under-estimation of risk. Although we could not control for potential confounding factors, our comparison within the veteran patient population probably minimized the effects of lifestyle factors such as alcohol and tobacco use [50]. Given the limitations of our study, the results must be interpreted judiciously.

The mechanisms by which obesity predisposes to cancer are likely to vary by the type of cancer. Metabolic alterations associated with obesity and excess abdominal fat may be related to the increased risk of some cancers, possibly through development of insulin resistance [55]. The precise mechanisms are unclear, but insulin resistance leads to an increase in circulating levels of insulin [56] and insulin-like growth factor-I (IGF-I) [3]. Both insulin and IGF-I inhibit the synthesis of sex hormone binding globulin (SHBG), lower levels of which may play a role in prostate cancer [37, 57]. In addition, the mitogenic and anti-apoptotic effects of insulin and IGF-I may contribute to elevated risks of prostate, colorectal and other cancers [3, 58, 59]. Although the relationship between IGF-I and RCC has not been reported in epidemiologic studies, renal cell tumor tissue has more IGF-I binding sites than adjacent normal kidney tissue [60]. In addition, there is some evidence suggesting that IGF-I stimulates the proliferation of bone marrow cells, and IGF-I receptors have been found in leukemic cells and cell lines [61]. Obesity may also impair immunologic responses [44, 62], thus predisposing to malignant melanoma or other tumors, as seen among transplant recipients with compromised immune function [63].

Certain lifestyle and behavioral factors that are correlated with obesity may also increase the risk for cancer, but could not be evaluated in our study. Most important is physical inactivity, which has been linked to increased risks of cancers of the colon, breast and prostate [64–66], and nutritional factors such as high-calorie and high-fat diets [19]. As noted previously, obesity has been associated with gastroesophageal reflux disease and Barrett's esophagus, which predisposes to esophageal adenocarcinoma [14], and with gallstones, which predispose to biliary tract cancer [30].

In summary, our cohort of clinically obese veterans confirms the associations previously established between obesity and risk for cancers of the lower esophagus, gastric cardia, colon, gallbladder, kidney, and prostate. We also provided additional evidence for links suggested between obesity and other cancers, including the small intestine, rectum, connective tissue, melanoma, male breast, thyroid and multiple myeloma. In addition, we identified obesity-related risks for various subsites of the colon, small bowel and biliary tract, and for subtypes of leukemia (AML and CLL). Few differences between white and black men were seen with respect to obesity-related patterns of cancer risk. In view of the global increase in the prevalence of obesity, further investigation is needed to clarify the impact of excess body weight on various forms of cancer and to elucidate the mechanisms involved.

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